Watch-and-wait in rectal cancer: A critical appraisal of promise, perils and unresolved contours of organ preservation (Review)

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Abstract. Total neoadjuvant therapy has elevated pathological complete response (pCR) rates in locally advanced rectal cancer to unprecedented levels (25-30%), catalyzing interest in organ preservation via the non-surgical 'Watch-and -Wait' (WaW) strategy. Although this approach offers a paradigm shift, its rapid clinical adoption necessitates a critical appraisal of unresolved controversies. The present review synthesizes current evidence to outline the benefits of WaW while critically examining its inherent challenges. A comprehensive analysis interrogates the dualistic nature of WaW. It can provide favorable survival (5-year overall survival of 85% and cancer-specific survival of 94% in the International WaW Database) and meaningful quality-of-life improvements by avoiding radical surgery; concurrently, it embodies substantial risks due to the inherent imprecision of clinical complete response (cCR) assessment (a 10-25% discordance with pCR), a marked local regrowth rate (~25%) and unresolved long-term oncological uncertainties. In the present review it is argued that successful implementation of WaW depends on transcending current limitations through technological integration. Circulating tumor DNA is a promising but still investigational biomarker that may enable dynamic risk stratification; however, its clinical utility requires prospective validation. In conclusion, WaW has evolved from a radical concept to a reasonable, evidence-supported option within a precision oncology framework for a meticulously selected patient cohort, contingent upon rigorous multidisciplinary team assessment and an unwavering, structured surveillance protocol. Its future safety and efficacy will be defined by advances in response assessment, personalized monitoring and long-term outcome data.

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Contents

1. Introduction

The management of locally advanced rectal cancer (LARC) has long been anchored by total mesorectal excision (TME) following neoadjuvant chemoradiotherapy (CRT) (1,2). This approach successfully curtailed local recurrence rates but at the cost of marked functional morbidity and permanent stomas in up to 30% of patients (3,4). The 21st century ushered in the era of total neoadjuvant therapy (TNT) (5,6), which not only addresses micrometastases earlier but also drives pathological complete response (pCR) rates to 25-30% (7), as demonstrated in trials such as OPRA (8). This breakthrough prompted a critical question; for patients achieving a clinical complete response (cCR) after TNT, is mandatory radical surgery always necessary, or could it represent overtreatment in some cases?

Pioneered by Habr-Gama *et al* (9), the watch-and-wait (WaW) strategy challenges the surgical dogma, offering a pathway to preserve rectal function and potentially enhance quality of life (QoL) (10). However, this path is complicated by the central conundrum of clinical assessment ambiguity and tumor biological heterogeneity. The traditional cCR evaluation toolkit, digital rectal exam, magnetic resonance imaging (MRI) and endoscopy, carries a non-negligible false-negative rate, while the long-term fate of clinically 'vanished' tumors remains only partially charted (11).

In the current treatment landscape, LARC management typically integrates neoadjuvant CRT or TNT, followed by TME as the standard surgical component. In parallel, emerging modalities such as immunotherapy (particularly for mismatch repair-deficient tumors) and targeted agents are reshaping therapeutic algorithms (12-16). The present review aimed to critically deconstruct the 'pros' and 'risk' dimensions of the WaW strategy by synthesizing the latest evidence, evaluating emerging biomarkers such as circulating tumor DNA (ctDNA) and proposing data-driven considerations. The current review presents that technology-facilitated precision in patient selection and dynamic risk monitoring is pivotal to mitigating risks and maximizing benefits (17,18). Therefore, the present article provides a critical analysis of the WaW strategy by interrogating key tensions: The balance between organ preservation and oncological safety; the limitations and evolving technologies in clinical response assessment; the management and implications of local regrowth; and the practical challenges of implementing rigorous surveillance protocols.

2. Methods for the literature search

Given the narrative nature of the present review, a systematic literature search was performed to ensure transparency. The databases PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://www.webofscience.com) and the Cochrane Library (https://www.cochranelibrary.com/) were searched for articles published between January 2000 and December 2025 using the following terms: 'Rectal cancer', 'watch-and-wait', 'total neoadjuvant therapy', 'clinical complete response', 'organ preservation', 'ctDNA' and 'local regrowth'. Included manuscripts were original articles, systematic reviews, randomized controlled trials (RCTs) and large registry studies reporting oncological or QoL outcomes in English. The reference lists of included articles were also screened for additional relevant studies. This approach, while not systematic in the strictest sense, provides a reproducible framework for the evidence synthesis presented.

3. Evolution of evidence for organ preservation: From clinical trials to real-world practice

The journey toward mainstream acceptance of WaW is underpinned by a sequential body of evidence, evolving from hypothesis-generating cohort studies to RCTs and large-scale real-world registries.

Pioneering observational studies and the proof of concept. The foundational hypothesis was posited by Habr-Gama *et al* (9), whose 2004 prospective observational study of 265 patients (71 achieving cCR managed non-operatively vs. 22 pCR patients undergoing surgery) demonstrated, with a mean follow-up of ~4 years, that patients with a sustained cCR after CRT could achieve excellent long term outcomes without immediate surgery (5-year OS, 100 vs. 88%; 5-year DFS, 92 vs. 83%), with salvage therapy effectively managing the minority who experienced local regrowth (9,19). This work challenged the surgical imperative and established the essential framework for patient selection and intensive surveillance.

Role of RCTs: Establishing comparative efficacy. While RCTs directly comparing WaW to standard TME in patients with cCR are ethically unacceptable (randomizing cCR patients to radical surgery without proven benefit) and practically infeasible (requiring thousands of patients due to >85% survival in both arms), several pivotal trials have provided indirect but powerful evidence supporting organ preservation.

GRECCAR 2 trial. This phase III RCT directly tested a more conservative surgical approach (local excision vs. TME) in good responders after CRT. Although its primary composite endpoint (death, recurrence, major morbidity) was not met (56 vs. 48%; P=0.43), it highlighted the importance of accurate response assessment and showed that organ-preserving strategies could be feasible in a subset of patients, setting the stage for non-operative management (4).

Trials of TNT. Modern RCTs of TNT regimens, such as RAPIDO (20), PRODIGE 23 (21) and OPRA (8), were designed to improve systemic disease control with mandated surgery for all participants (6,7). However, a critical secondary finding was the marked increase in pCR rates (28-30%) compared with standard chemoradiotherapy (6-8). This phenomenon is of notable importance for organ preservation, as it substantially enlarges the population of patients who may achieve cCR after TNT and thus become potential candidates for a non-operative WaW strategy. The OPRA trial specifically used organ preservation as a primary endpoint, demonstrating that a TNT-first approach could successfully spare nearly half of the patients from radical resection without compromising 3-year disease-free survival, while RAPIDO and PRODIGE 23 reported significantly improved 3-year disease-free survival and higher pCR rates compared with standard chemoradiotherapy (8,20,21).

Synthesis of real-world evidence: Validation and refinement. Large-scale prospective registries have been instrumental in translating trial findings into clinical practice, addressing questions of generalizability and long-term safety. While most evidence supports the oncological safety of W&W in strictly selected patients, a small number of real-world studies have raised concerns, including a Norwegian population-based study that reported higher than expected local regrowth (53%) and metachronous metastases (14%) rates among patients with cCR (22).

International WaW database (IWWD). As the largest pooled registry, its analysis of nearly 1,000 patients provided the first high-quality, multicenter evidence on oncological outcomes. The reported 5-year overall survival of 85% and cancer-specific survival of 94% for patients with cCR offered powerful validation of the safety of the strategy in a real-world, non-selected cohort (23).

Propensity-matched cohort studies. Studies such as that by Smith *et al* (24) performed rigorous statistical matching between patients treated by WaW and patients treated with surgery with a pCR (24). Their finding of equivalent survival outcomes provides the strongest non-randomized comparative evidence to date, effectively mitigating concerns about survival trade-offs, a conclusion further supported by the OnCoRe propensity-matched cohort (25).

National registry analyses. Studies from national cancer databases (such as the Netherlands Cancer Registry, the Chinese Watch-and-Wait Database) have corroborated these findings on a population level, confirming that WaW outcomes are reproducible outside expert centers (26,27) (Table I).

Evolving consensus: From 'if' to 'how'. The convergence of evidence from RCTs and real-world studies has shifted the clinical discourse. The question is no longer if WaW is a valid strategy for selected patients, but how to implement it optimally. This involves refining patient selection through improved biomarkers (such as ctDNA), standardizing response assessment with artificial intelligence and personalizing surveillance intensity.

4. Favorable outcomes: The case for organ preservation

Oncological outcomes: Evidence from large datasets. Early skepticism toward WaW focused primarily on its oncological safety. Today, long-term follow-up data from large international registries provide a robust response. The IWWD, in a pooled analysis of 867 patients with cCR, demonstrated a 5-year overall survival rate of 85% and a cancer-specific survival rate of 94% (23). These outcomes are comparable to those observed in patients who achieve a pCR and undergo standard TME surgery [e.g., Smith *et al* (24) reported 5-year OS of 94% in the pCR group]. This indicates that for the cohort of patients who truly achieve cCR, delaying or even avoiding surgery does not confer a survival disadvantage in the mid-term.

A large 2019 multicenter propensity score-matched analysis further corroborates this view. Comparing patients treated by W&W from several leading cancer centers with patients with pCR who underwent standard TME surgery (113 W&W patients matched to 136 patients with pCR) (24). Comparing patients treated by WaW from several leading cancer centers with patients with pCR who underwent standard TME surgery, the study found that after propensity score matching, the 3-year overall survival and metastasis-free survival rates were markedly similar between the two groups (3-year OS: 92.4% in W&W vs. 95.0% in pCR; 3-year MFS: 88.9 vs. 92.9%; P-value not significant for both) (24). This accumulating real-world evidence is gradually dismantling the traditional dogma that 'only surgical resection can cure' (25) (Table II).

Hierarchy of oncological endpoints in WaW. It is important to distinguish between endpoints when interpreting these results. Overall survival and cancer-specific survival (CSS) are the most robust measures of oncological safety (28). Disease-free survival (DFS) and local regrowth rates are secondary endpoints; favorable DFS or regrowth-free survival does not automatically equate to long-term overall survival equivalence (29). Currently, most WaW data support overall survival and CSS up to 5 years; definitive evidence beyond 10 years remains limited (30).

QoL: A multidimensional benefit. While oncological safety is the non-negotiable foundation, the potential advantage of WaW lies in its ability to deliver improvement in patient QoL. This extends beyond the mere avoidance of a stoma; it represents a comprehensive preservation of pelvic anatomical and functional integrity. Evidence from prospective QoL studies using validated instruments (EORTC QLQ-C30, CR38, LARS score) consistently demonstrates a multifaceted benefit. For example, a prospective cohort study of 278 patients (221 W&W, 18 local excision, 39 TME) reported that W&W patients had good QoL and significantly less major bowel dysfunction than those requiring surgery (25 vs. 56% after local excision and higher rates after TME) (31). The most immediate and tangible benefit is the circumvention of major colorectal resection and its associated sequelae.

Avoidance of permanent stoma. For patients who would otherwise require an abdominoperineal resection, WaW eliminates the lifelong physical and psychological burden of a permanent colostomy. Studies report notably higher scores in body image and social functioning domains for patients treated by WaW compared with patients with stoma (mean difference of +15 to +20 points on relevant EORTC subscales) (32,33).

Prevention of low anterior resection syndrome (LARS). Even with sphincter-preserving low anterior resection, up to 80% of patients experience LARS, a debilitating cluster of symptoms including fecal incontinence, urgency and clustering. By forgoing any rectal resection, patients treated by WaW maintain near-normal bowel continence and function. Severe LARS is virtually absent in the WaW cohort, whereas it affects 25-40% of patients after LAR (31).

Reduction in surgical complications. WaW avoids the risks of anastomotic leakage (5-15%), pelvic sepsis and re-operation inherent to TME surgery, along with prolonged hospitalizations and recovery periods (34,35).

Protection of genitourinary and sexual function. Surgical dissection within the narrow confines of the pelvis carries a high risk of injury to the autonomic nerve plexi responsible for bladder control and sexual function. WaW obviates this iatrogenic injury at its source. Post-operative sexual dysfunction, particularly erectile dysfunction in men and dyspareunia in women, is common. A prospective study found that in men, impotence occurred in 32%, partial impotence in 52%; in women, dyspareunia occurred in 46% and lubrication difficulties in 56% (36). A long-term study by Custers *et al* (31) found that >85% of men in a WaW cohort preserved erectile function, compared with rates often below 30-40% in historical surgical series. In addition, bladder voiding dysfunction and urinary incontinence are notably less prevalent in patients treated by WaW, who are spared injury to the pelvic splanchnic nerves and hypogastric plexus. A 2024 meta-analysis of 55 studies including 15,072 patients reported that 25% of patients experienced urination dysfunction ≥12 months after rectal cancer surgery, with long-term incontinence (23%) and difficulty in bladder emptying (30.6%) as common complications (37,38).

Psychosocial well-being and the 'burden of surveillance'. The holistic impact extends into psychological and social domains. Without the physical trauma of major surgery and the constant reminder of a stoma or bowel dysfunction, patients often experience a qualitatively different recovery. Avoidance of a permanent alteration in body function may mitigate risks of anxiety, depression and social isolation (39). However, the WaW pathway is not without psychological demands. The intensive surveillance schedule and the ever-present, albeit low, risk of regrowth can generate 'scan anxiety' and a state of chronic

Table I. Key clinical studies shaping the organ preservation paradigm.

Study (year)	Design	Key intervention/group	Primary finding relevant to WaW	Evidence level/key details	(Refs.)
Habr-Gama *et al*, 2004	Prospective cohort	CRT → cCR → WaW	Demonstrated feasibility and safety of non-operative management	Hypothesis-generating. n=265; 71 cCR patients (26.8%) managed with W&W; median follow-up 57.3 months; 5-year OS 100% in W&W vs. 88% in pCR resection group; 5-year DFS 92 vs. 83%; no stomas in W&W vs. 9 permanent colostomies in resection group.	(9)
GRECCAR 2, 2017	Phase III RCT	Local excision vs. TME (good responders)	Highlighted challenge of response assessment; supported selective organ preservation	Level I (for local excision). n=148; primary endpoint (composite of death, recurrence, major morbidity at 2 years) not met (56 vs. 48%; OR 1.33, 95% CI 0.62-2.86; P=0.43); 5-year follow-up showed local excision non-inferior to TME for local recurrence and OS.	(4)
RAPIDO, 2020	Phase III RCT	Short-course RT + TNT vs. CRT	Notably increased pCR (28% vs. 14%), expanding pool for WaW	Level I. n=920; pCR rates: 28% (120/423) in TNT group vs. 14% (57/398) in CRT group (OR 2.37, 95% CI 1.67-3.36, P<0.001); 3-year DFS improved in TNT group (76 vs. 68%).	(20)
OPRA, 2022	Phase II RCT (organ preservation endpoint)	TNT → cCR → WaW	3-year DFS identical whether cCR achieved via chemo-first or CRT-first TNT	Prospective validation. n=292; 3-year DFS 76% in both arms; organ preservation rate 41% (INCT-CRT) vs. 53% (CRT-CNCT); salvage TME successful in >85% of regrowths.	(8)
IWWD, 2018	International registry	Pooled patients with cCR from >30 centers	Provided robust real-world 5-year survival benchmarks (OS 85%, CSS 94%)	Large-scale RWE. n=867; median follow-up 3.3 years; 5-year OS 85% (95% CI 80-90%), CSS 94% (95% CI 91-97%); 2-year cumulative local regrowth rate 25%; 80% of regrowths occurred within first 2 years.	(23)
Smith *et al*, 2019	Propensity-matched analysis	WaW (cCR) vs. TME (pCR)	No difference in 3-year OS or DMFS between matched groups	Comparative RWE. n=113 W&W matched to 136 pCR patients; 3-year OS: 92.4% (W&W) vs. 95.0% (pCR); 3-year DMFS: 88.9% vs. 92.9%; P=NS for both; median follow-up 38 months.	(24)

RCT, randomized controlled trial; WaW, watch-and-wait; cCR, clinical complete response; pCR, pathological complete response; OS, overall survival; CRT, chemoradiotherapy; DFS, disease free survival; TNT, total neoadjuvant therapy; DMFS, distant metastasis-free survival; RWE, real-world evidence; NS, not significant.

uncertainty for some patients. Prospective QoL studies generally indicate that this burden of surveillance is, for most, preferable to the definite and permanent functional losses imposed by radical surgery (32). This underscores the importance of thorough patient counseling and shared decision-making, ensuring that candidates are not only clinically suitable but also psychologically prepared for the WaW journey.

In summary, the QoL argument for WaW is multi-dimensional. It is not merely an ancillary benefit but a core outcome

Table II. Comparative oncological outcomes of WaW vs. standard TME in patients with cCR/pCR.

Study (year)	Patient group	Sample size, n	Follow-up, years	OS, %	Disease-free survival, %	Local regrowth/ recurrence rate, %	Key conclusion	(Refs.)
IWWD, 2018	WaW (cCR)	867	3	91	87	25 (2-year cumulative)	Excellent OS/CSS; most regrowths early and salvageable	(23)
Smith *et al*, 2019	WaW (cCR) vs. TME (pCR)	113 vs. 136 (matched)	3	~95 vs. ~95	~88 vs. ~89	Not directly compared	Notably comparable survival outcomes between strategies	(24)
OPRA Trial, 2022	WaW post-TNT	292	3	91	76	~25	TNT followed by WaW provides satisfactory organ preservation without compromising survival	(8)

WaW, watch-and-wait; OS, overall survival; CSS, cancer-specific survival; TNT, total neoadjuvant therapy; cCR, clinical complete response; pCR, pathological complete response; TME, total mesorectal excision.

that redefines the therapeutic goal in rectal cancer management, from survival at any cost to survival with optimal function and dignity.

Evolution of the treatment paradigm. The increasing prevalence of WaW signifies a fundamental shift in the philosophy of rectal cancer treatment, moving from 'maximal tolerable therapy' toward 'minimal effective therapy'. Using TNT as an *in vivo* biopsy, biological subtypes of tumors that are notably sensitive to CRT can be screened for. Resecting an organ that has effectively been 'cured' *in situ* can, in a sense, be viewed as overtreatment (40). WaW thus represents an application of precision medicine in the surgical management of solid tumors (41). Despite these encouraging data, it is critical to recognize that comparative survival evidence largely stems from non-randomized studies with inherent selection bias. The favorable QoL outcomes, while compelling, must be weighed against the psychological burden of intensive surveillance, a trade-off that requires further patient-centered research.

5. Calculated risk: Challenges and perils

Weaknesses of cCR assessment. Currently, the determination of cCR is a clinical composite judgment, typically based on digital rectal examination, MRI and high-resolution endoscopy (42,43) using criteria such as those from Memorial Sloan Kettering Cancer Center (44) However, this system has inherent limitations.

Limitations of MRI. While diffusion-weighted imaging provides functional information, the resolution of MRI for detecting residual microscopic tumor foci, particularly within the bowel wall, is limited. Meta-analyses indicate that the false-negative rate of cCR assessment (cCR without pCR) lies within a range of 10-25% (10,23,45).

Blind spots of endoscopy and biopsy. The submucosa underlying endoscopically normal-appearing mucosa may harbor tumor cells. Random biopsies suffer from notable sampling error and cannot represent the entire tumor bed (43,46).

Advances. To break through this bottleneck, research is focusing on artificial intelligence (AI)-assisted image analysis (47) and quantitative radiomics. Deep learning models that analyze texture features imperceptible to the human eye in MRI images promise more accurate prediction of tumor regression (43). Furthermore, new techniques such as endoscopic contrast-enhanced ultrasound are being explored to improve assessment accuracy (48-50).

Local regrowth

A major clinical endpoint in the W&W strategy. Local regrowth represents the most common and clinically significant adverse event following a watch-and-wait approach (51). According to IWWD data (23), the cumulative 2-year local regrowth rate is ~25%, with the majority (~80%) of these events occurring within the first 24 months of surveillance (Fig. 1).

Analysis of regrowth patterns brings a positive signal, and ~90% of regrowths are local, non-invasive and usually occur at the primary tumor site (intraluminal regeneration). Notably, the majority (>85%) of these regrowths can be curatively treated with timely salvage TME surgery (52,53), and long-term survival rates after salvage surgery are comparable

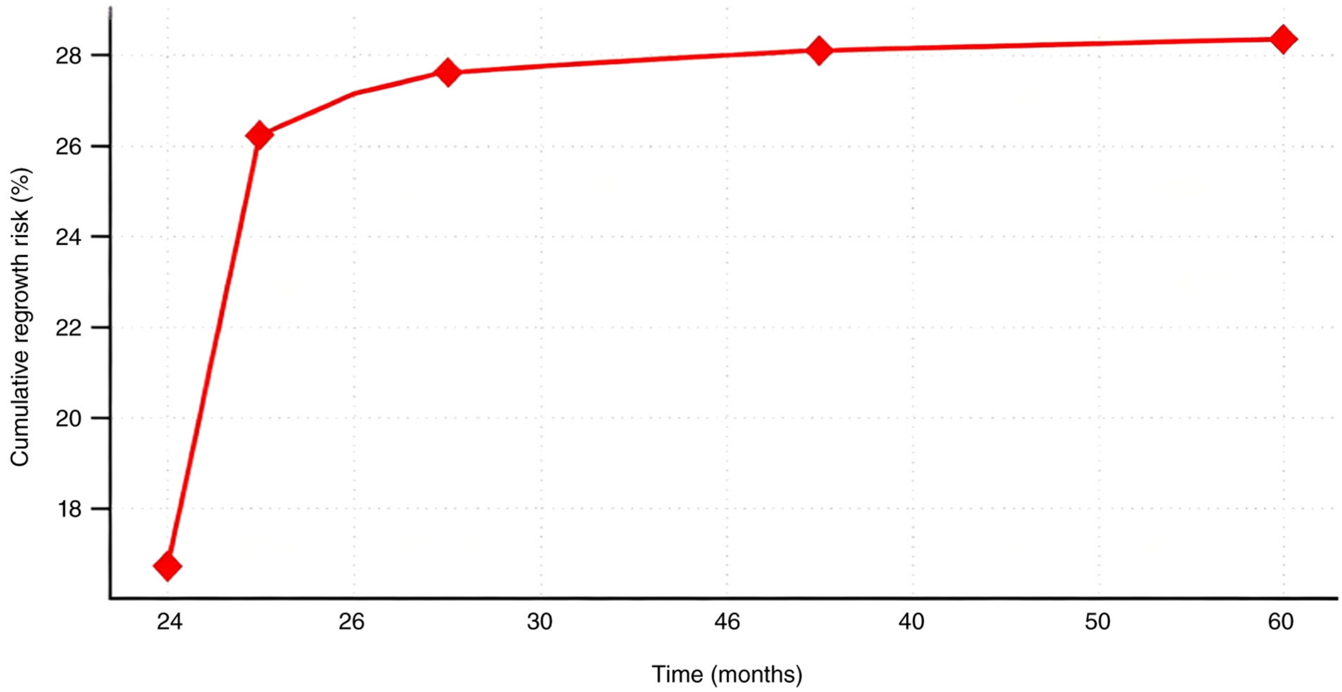

Figure 1. Cumulative risk of local regrowth over time in a watch-and-wait cohort. Data from the international watch-and-wait database showing cumulative local regrowth rates at selected time points. The cumulative risk increases from 24.5% at 6 months to 28.1% at 46 months, with the majority of regrowth events occurring within the first 2 years of surveillance. This figure is derived from the pooled analysis of 867 patients with clinical complete response following neoadjuvant therapy (14).

with those of patients who had initial surgery. This underscores the importance of early detection, which relies entirely on a strict follow-up protocol (54,55).

Strategies to mitigate regrowth risk. Risk-stratified surveillance intensity based on initial response depth is a promising approach (54). Patients with a 'deep' cCR (complete normalization of MRI and endoscopy with negative ctDNA) might be eligible for less intensive follow-up, whereas those with 'near-cCR' could be considered for consolidative local therapies (such as local excision) within clinical trials (26). Emerging evidence suggests that ctDNA may help identify patients at highest risk of early regrowth, enabling closer monitoring or prophylactic intervention (56), although this remains investigational.

Long-term doubts and occult metastasis: Exploring the unknown. Despite encouraging mid-term data, long-term oncological outcome data beyond 10 years for the WaW strategy remain scarce (57). There is concern about the possibility of occult residual disease in unresected mesorectal lymph nodes acting as 'seeds' for future distant metastasis (58).

ctDNA. Liquid biopsy, particularly ctDNA detection, is considered a potential tool for this dilemma (41). ctDNA can detect trace amounts of DNA fragments from tumor cells in the blood, with assays capable of detecting mutations at a variant allele frequency as low as 0.01%, far below the spatial resolution of traditional imaging (59). Studies show that patients with persistently positive ctDNA after TNT have a markedly high risk of recurrence; such patients are likely unsuitable for the WaW strategy. For patients with cCR who become ctDNA-negative after TNT and enter the WaW pathway, periodic ctDNA monitoring may serve as a sensitive 'liquid sentinel'. A reconversion of ctDNA to positivity often occurs months before radiological or endoscopic detection of recurrence (60,61), providing a valuable window for intervention.

Nevertheless, ctDNA remains investigational in this setting. Standardized assays, validated thresholds and prospective trials demonstrating its utility as a standalone decision-making tool are still needed. The future WaW model will likely be a tripartite precision monitoring system integrating clinical assessment, imaging and ctDNA (Fig. 2), but this remains a hypothesis-generating framework requiring prospective validation. The challenges outlined here underscore that WaW is not a passive strategy but an active, high-stakes management plan.

6. Precision frontier: Microsatellite instability-high (MSI-H) rectal cancer and immunotherapy-driven organ preservation

A critical dimension absent from the earlier discussion of TNT and WaW is the distinct biological subset of MSI-H or mismatch repair-deficient (dMMR) rectal cancers, which account for 5-10% of non-metastatic cases (62). The management of this subgroup is undergoing a radical transformation, potentially redefining the concept of neoadjuvant therapy and organ preservation (63).

A unique biology with marked therapeutic sensitivity. MSI-H tumors harbor a high mutational burden and a robust tumor-infiltrating lymphocyte presence, rendering them notably sensitive to immune checkpoint inhibitors (ICIs), such as anti-PD-1 antibodies (pembrolizumab and dostarlimab).

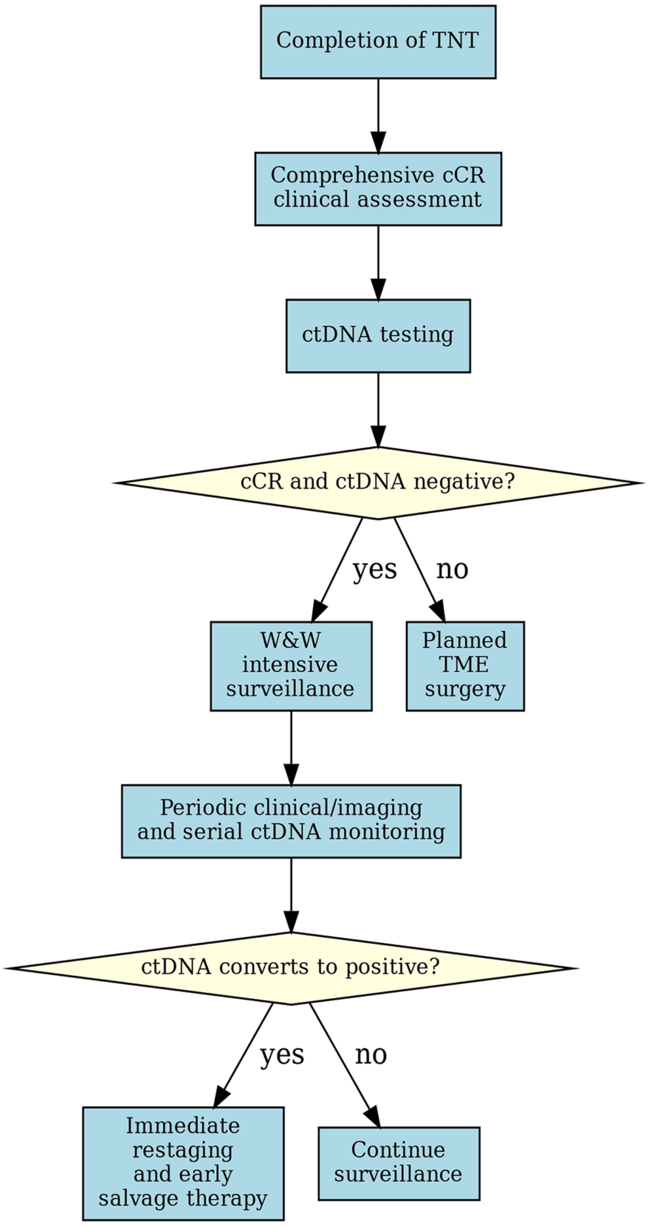

Figure 2. Proposed ctDNA-guided precision management pathway for watch-and-wait. Hypothetical algorithm integrating post-TNT ctDNA testing and serial monitoring into the watch-and-wait decision-making process. Following completion of TNT and comprehensive cCR assessment, patients with cCR and negative ctDNA enter the watch-and-wait surveillance protocol. Patients with persistent ctDNA positivity (regardless of cCR status) are referred for planned TME. During surveillance, conversion of ctDNA to positivity triggers immediate comprehensive restaging and early salvage therapy. This framework remains investigational and requires prospective validation before clinical implementation. TNT, total neoadjuvant therapy; TME, total mesorectal excision; cCR, clinical complete response.

Unlike conventional chemotherapy and radiotherapy, ICIs can induce deep and durable antitumor immune responses (64).

Pioneering clinical evidence: Dawn of 'chemo-radiation-free' curative intent therapy. Emerging clinical trial data suggest that neoadjuvant immunotherapy alone may be sufficient for achieving curative outcomes in locally advanced MSI-H rectal cancer, challenging the necessity of cytotoxic therapy or radiation. While focusing on colon cancer, the NICHE study demonstrated a 100% pathological response rate (660% pCR) (65) to neoadjuvant nivolumab + ipilimumab in patients with dMMR. This principle is being actively translated to rectal cancer (66). Numerous phase II studies investigating neoadjuvant pembrolizumab monotherapy in MSI-H LARC have reported cCR rates of 60-70% and pCR rates of 50-60% after several cycles of treatment, with minimal toxicity (62,67).

A notable single-arm, phase II trial (NCT04165772) evaluated neoadjuvant dostarlimab in patients with dMMR, locally advanced rectal adenocarcinoma (68). In an interim analysis, all evaluable patients (12/12) who completed the planned 6-month course achieved a cCR, with no evidence of tumor on MRI, fluorodeoxyglucose-PET, endoscopic evaluation or digital rectal examination. None of the patients required subsequent CRT or surgery, and no cases of progression or recurrence were reported during follow-up. At the time of interim analysis, the median follow-up duration was 6.8 months (range, 0.7-23.8 months) (68).

These response rates, particularly the 100% cCR rate with dostarlimab, challenge the necessity of cytotoxic therapy or radiation for this molecular subset. This raises the possibility of a 'chemo-radiation-free and surgery-free' curative pathway for selected patients with MSI-H. The WaW strategy in this context evolves from a post-chemoradiation option to the primary intended management following neoadjuvant immunotherapy alone.

Integration into the WaW framework: New opportunities and unanswered questions. The integration of MSI-H management into organ preservation strategies necessitates novel considerations. Patient selection-including confirmation of dMMR/MSI-H status by immunohistochemistry or PCR, and exclusion of metastatic disease-requires universal MSI/MMR testing at diagnosis to identify candidates for this paradigm. Patterns of response to immunotherapy (such as pseudoprogression, delayed response) differ from those seen with CRT, as immunotherapy can manifest unique response patterns, including pseudoprogression and delayed tumor regression. The definition of cCR and optimal imaging modalities require re-evaluation. In addition, the role of ctDNA for monitoring post-immunotherapy is of interest but not yet standardized. Ongoing randomized trials (such as comparing immunotherapy-based TNT to standard CRT-based TNT in patients with MSI-H) will provide Level I evidence to solidify this approach.

In summary, the MSI-H subtype represents the vanguard of truly biomarker-driven, response-adapted organ preservation in rectal cancer. It illustrates the future direction of the field: Moving beyond a 'one-size-fits-all' TNT approach toward personalized neoadjuvant strategies where the choice of therapy, and the possibility of WaW, is dictated by the fundamental molecular characteristics of the tumor (Table III).

7. Towards consensus: Balancing hope and risk

Confronting both potential benefits and risks, the international academic community is converging on a consensus: WaW is not a binary option but a nuanced strategy to be offered to carefully selected patients within a markedly structured pathway (57).

Table III. Evolving neoadjuvant strategies for MSI-H locally advanced rectal cancer and their organ preservation potential.

Strategy	Therapeutic agents	Reported pCR/cCR rate, %	Key advantages	Challenges and unknowns
Standard CRT-based TNT	Fluoropyrimidine + Radiation → Chemo	25-30	Established safety profile, long-term data	Likely 'over-treatment' for this sensitive subtype; excess toxicity
Immunotherapy-based TNT	Anti-PD-1 ± other agents → (chemo/RT)	50-70 (early data)	Exceptional efficacy, less acute toxicity, systemic immune activation	Long-term durability of response? Optimal treatment duration?
Immunotherapy alone	Anti-PD-1 monotherapy	~60 cCR (early data)	Maximally de-escalated; avoids all cytotoxic therapy toxicity	Definitive efficacy vs. combination approaches? Optimal patient selection?

cCR, clinical complete response; pCR, pathological complete response; CRT, chemoradiotherapy; MSI-H, microsatellite instability-high; TNT, total neoadjuvant therapy.

Patient selection and structured follow-up

Ideal candidate selection. Baseline tumor characteristics include: Initial stage T2-3 (some selected T4a), N0-1, no distant metastasis and no extramural vascular invasion. The patient should display excellent response to TNT, strictly meeting cCR criteria. In addition, the patient needs to understand the procedure and provide full informed consent, high compliance and commitment to completing the intensive follow-up plan (Table IV).

Central role of the multidisciplinary team (MDT). The determination of cCR and the subsequent decision to embark on a WaW pathway is a high-stakes clinical judgment that should not be rendered by a single specialist. International consensus guidelines uniformly mandate that this decision should arise from a formal consensus deliberation by a specialized MDT (54). An effective rectal cancer MDT for this purpose should, at a minimum, include colorectal surgeons, medical oncologists, radiation oncologists, dedicated abdominal radiologists and gastrointestinal pathologists. This collaborative synthesis is a notable safeguard against the inherent limitations and subjectivity of any single assessment modality (42,43). Studies have shown that MDT review changes management plans in a notable proportion of complex rectal cancer cases, improving staging accuracy and adherence to treatment guidelines (69-72). Therefore, MDT consensus is a non-negotiable prerequisite for safe entry into a WaW program.

Structured follow-up protocol. The safety of the WaW strategy is contingent upon an unwavering, protocol-driven surveillance schedule designed for early detection of local regrowth. There is broad international consensus on an intensive schedule that de-escalates over time (54,57). Years 1-2 (high-risk period): Assessments every 2-3 months, including clinical history, digital rectal examination, serum carcinoembryonic antigen (CEA), high-resolution pelvic MRI (with diffusion-weighted imaging) and rigid or flexible proctoscopy (23,54,55). This high frequency is justified by the observation that ~80% of local regrowths occur within the first 24 months after treatment completion (23). Years 3-5: Interval can be safely extended to every 6 months, maintaining the same combination of clinical, biomarker and imaging assessments (54). After 5 years: Annual surveillance is generally considered sufficient, mirroring the long-term follow-up for patients who underwent curative resection (40,54).

Integrating ctDNA into surveillance: Technical considerations and investigational status. The incorporation of ctDNA analysis holds transformative potential for personalizing and enhancing the safety of WaW surveillance. However, its implementation requires a nuanced strategy and an understanding of available technologies. It is important to emphasize that ctDNA monitoring remains an investigational tool and is not yet incorporated into formal clinical guidelines; its use should be within clinical trials or institutional protocols.

Proposed ctDNA monitoring strategy. A rational, evidence-informed approach involves three key timepoints (41,60,73): Baseline (post-TNT): Obtain a plasma sample 4-8 weeks after completing TNT. A negative ctDNA result is a favorable prognostic marker, supporting the decision for WaW. A persistently positive result notably predicts residual disease and imminent recurrence; such patients should be strongly reconsidered for immediate salvage TME surgery. During active surveillance (years 1-2): Perform serial testing every 3-4 months, synchronized with clinical and imaging visits. The goal is to monitor for molecular recurrence (ctDNA reconversion from negative to positive), which typically precedes radiographic detection of regrowth by 3-6 months. At suspicion of recurrence: In cases of ambiguous imaging or clinical findings, a contemporaneous ctDNA test can serve as a markedly specific 'liquid biopsy' to clarify the likelihood of true disease recurrence vs. post-treatment change.

Technical approaches to ctDNA detection: Pros and cons. Table V compares the main ctDNA assay types. For the WaW setting, where the clinical question is the detection of minimal residual disease and early molecular recurrence, the

Table IV. Ideal candidate selection criteria for a watch-and-wait strategy.

Dimension	Ideal criteria	Cautionary/exclusionary criteria
Baseline tumor	cT2-3b, cN0-1, no EMVI, no lateral pelvic node involvement	cT4a/b, cN2, presence of EMVI, low-lying tumors with sphincter invasion
Treatment response	Excellent response to TNT, meeting stringent cCR criteria (such as MSKCC criteria)	Near-cCR, residual small ulceration or nodule
Patient factors	Comprehensive informed consent, high compliance, commitment to intensive follow-up	Poor psychological resilience, anticipated low follow-up adherence
Biomarkers (emerging)[a]	ctDNA clearance post-TNT	Persistently positive ctDNA post-TNT

[a]The use of biomarkers (such as ctDNA) for patient selection is emerging and rapidly evolving; it is not yet a standardized component of most formal guidelines and should be applied within clinical trials or with institutional protocol support where available. pCR, pathological complete response; CRT, chemoradiotherapy; TNT, total neoadjuvant therapy; ctDNA, circulating tumor DNA; EMVI, extramural vascular invasion; MSKCC, Memorial Sloan Kettering Cancer Center.

Table V. Comparison of primary ctDNA testing strategies in the WaW context.

Assay type	Methodology	Pros	Cons	Best suited for
Tumor-informed, patient-specific (such as Signatera™)	Custom-designed PCR or NGS assay targeting 16-50 somatic variants unique to the patient's tumor (from archival tissue)	Highest sensitivity and specificity; can detect minute quantities of ctDNA (limit of detection ~0.01%); quantitative tracking of variant allele frequency	Requires tumor tissue; longer turnaround time; higher cost	Optimal for MRD monitoring where ultra-sensitivity is critical
Tumor-agnostic, fixed panel (such as Guardant Reveal™)	NGS panel targeting a fixed set of genes and epigenetic markers common across cancers	No tumor tissue needed; faster, standardized workflow; can detect unknown/ novel mutations	Lower sensitivity for MRD; potential false positives from clonal hematopoiesis (CHIP)	Screening tool if tissue is unavailable; may be useful for detecting later, higher-volume recurrence
Methylation-based assays	Detects cancer-specific hypermethylation patterns in plasma cell-free DNA	High cancer-specificity; methylation changes are abundant and early in carcinogenesis; tissue-of-origin prediction possible	Clinical validity in rectal cancer WaW setting still under investigation; standardization evolving	Emerging modality; likely to be integrated into future multi-analyte panels

NGS, next generation sequencing; WaW, watch-and-wait; MRD, minimal residual disease; CHIP, clonal hematopoiesis of indeterminate potential.

tumor-informed, patient-specific approach currently offers the most robust performance characteristics, despite its logistical demands. As evidence matures and costs decrease, ctDNA monitoring may evolve from an investigational tool to a cornerstone of precision surveillance, but current use should be considered hypothesis-generating (Fig. 2).

Comprehensive informed consent. An honest discussion with the patient and family is mandatory, covering: The rationale for the WaW strategy, the precise risk of local regrowth, the success rates and risks of salvage surgery and an explanation of long-term uncertainties.

8. Conclusions and future directions: Towards a mature, risk-adapted organ preservation paradigm

The WaW strategy for rectal cancer stands at a pivotal juncture. It has demonstrated that for a biologically select group of patients achieving a cCR, organ preservation with oncological safety is an achievable goal in the mid-term. The accumulated evidence from registries and comparative studies confirms that WaW can deliver survival outcomes comparable to radical surgery up to 5 years, while offering a transformative improvement in QoL by preserving anorectal, urinary and sexual function. This firmly establishes it as a valid component of the modern therapeutic arsenal for locally advanced rectal cancer, but only for carefully selected patients within a structured program. However, as the present review has elucidated, current implementation of WaW is fundamentally constrained by its reliance on an imperfect, binary decision point, the cCR. This artifact of assessment leads to inevitable rates of local regrowth and perpetuates a 'one-size-fits-all' surveillance model. Therefore, the true future of organ preservation lies not in refining the cCR construct alone, but in orchestrating a shift toward dynamic, risk-adapted management. To navigate this shift and solidify WaW as a robust, equitable standard of care, several future directions must be prioritized.

Precision in selection and assessment. Prospective validation of ctDNA as a tool for confirming molecular complete response and monitoring for molecular recurrence is paramount (73). Simultaneously, AI and radiomics must be translated from research tools into clinical aids that standardize and objectify MRI-based response evaluation, reducing inter-observer variability. Integration of tissue-based biomarkers (such as Immunoscore, MSI/MMR status) will further refine upfront patient stratification.

Development of risk-stratified pathways. The next generation of clinical trials should move beyond simply offering WaW to all patients with cCR. They must test risk-adapted surveillance and intervention protocols. For instance, patients with a 'deep' clinical, radiological and molecular response could be enrolled in trials of de-intensified, less frequent follow-up. Conversely, those with 'near-cCR' or specific high-risk biologic features could be offered novel consolidative therapies (such as short-course immunotherapy, targeted agents) within clinical trials to increase their chances of successful organ preservation.

Implementation science and equity. Research must expand beyond academic centers to address pragmatic questions. Cost-effectiveness analyses comparing lifelong surveillance to upfront surgery are needed for healthcare system planning. Studies should also focus on implementation barriers, such as standardizing MDT protocols across community and tertiary settings and developing technological solutions (such as centralized AI imaging review, accessible ctDNA testing) to mitigate geographic and socioeconomic disparities in access to precision WaW programs.

Securing long-term data and patient-reported outcomes. Continued long-term follow-up (>10 years) of existing WaW cohorts remains essential to definitively confirm the non-inferiority of CSS. Equally important is the systematic collection of long-term patient-reported outcomes, capturing not only functional results but also the psychological experience of long-term surveillance, to fully understand the benefit-burden balance from the perspective of the patient.

In conclusion, the WaW strategy offers a promising alternative to radical surgery for selected patients (74), but it remains a calculated risk, with the calculation currently based on imperfect inputs. By embracing the aforementioned future directions focusing on precision biomarkers, risk-adapted pathways, equitable implementation and long-term data, the oncology community can transform this promising strategy into a mature, reliable and widely accessible pillar of rectal cancer care. The goal is no longer just to 'WaW', but to stratify, guide, and preserve with confidence.

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Authors' contributions

The present review was conceptualized by XQZ, BBG and LCW. The formal analysis was performed by XQZ, BBG and SWS. The literature search, data extraction, and synthesis was conducted by XQZ and LCW. Project administration was conducted by XQZ, BBG and SWS. XQZ and BBG wrote the original draft and reviewed and edited the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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